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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/892,505	06/28/2001	Saluh Kivlighn	50193-109	4997

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EXAMINER
KANTAMNENI, SHOBHA

ART UNIT	PAPER NUMBER
1617	

MAIL DATE	DELIVERY MODE
02/07/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/892,505	KIVLIGHN ET AL.	
	Examiner	Art Unit	
	Shobha Kantamneni	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *NONE* is/are allowed.

6)☒ Claim(s) *16-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/31/2007 has been entered.

In view of new ground(s) of rejections, the rejections made in the previous office action are herein withdrawn.

Currently, claims 16-18 are pending.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 16-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Maeda et al. (5,747,495, PTO-892), in view of Nakamoto et al. (EP 0 337 350, PTO-1449), and further in view of applicant's admission,

Maeda et al. discloses a method of treating hypertension comprising administering to a patient in need thereof a therapeutically effective amount of a uric acid lowering agent, a xanthine oxidase inhibitor, 4-amino-6-hydroxypyrazolol [3,4-d]pyrimidine (AHPP). See abstract; column 2, lines 11-13; column 6, Example 9, claim 1. For oral administration of AHPP, the effective antihypertensive amount is 100-9000 mg/day/adult patient. See column 2, lines 63-65. It is also taught that uric acid production was inhibited by AHPP in a dose dependant manner i.e xanthine oxidase inhibitor lowers uric acid in a dose dependent manner. See column 4, Example 5.

Maeda et al. do not explicitly teach the administration of a therapeutically effective amount of xanthine oxidase inhibitor to achieve a uric acid level in the patient of 4 to 6 mg/dl in treating hypertension.

Maeda et al. do not teach administration of a therapeutically effective amount of allopurinol to achieve a uric acid level in the patient of 4 to 6 mg/dl in treating hypertension.

Nakamoto et al. teaches that compounds that lower uric acid are effective in treating hypertension. Nakamoto et al. also teaches that allopurinol is a well known agent employed to lower uric acid. Further, Applicant acknowledges that uric acid was known as a possible risk factor for hypertension. See instant specification page 2, lines 10-11.

It would have been obvious to a person of ordinary skill in the art to determine the optimal parameters such as effective amounts of xanthine oxidase inhibitor needed to achieve desired results i.e uric acid level in the patient of 4 to 6 mg/dl in treating

hypertension because 1) Maeda et al. teaches that uric acid production was inhibited by xanthine oxidase inhibitor, AHPP in a dose dependent manner, 2) Nakamoto et al. teaches that compounds that lower uric acid are effective in treating hypertension, and 3) Applicant acknowledges that uric acid was known as a possible risk factor for hypertension. Accordingly, one of ordinary skill in the art at the time of invention would have been motivated to optimize the amount of uric acid lowering agents, xanthine oxidase inhibitors to achieve uric acid levels of 5.0-6.9 mg/dL with reasonable expectation of success of treating hypertension, since as discussed above and further applicant also acknowledges that uric acid was known as a possible risk factor for hypertension.

It would have been obvious to a person of ordinary skill in the art at the time of invention to administer therapeutically effective amount of allopurinol to achieve a uric acid level in the patient of 4 to 6 mg/dl in treating hypertension.

One of ordinary skill in the art at the time of invention would have been motivated to administer allopurinol with reasonable expectation of success of treating hypertension by lowering uric acid because 1) applicant acknowledges that uric acid was known as a possible risk factor for hypertension and 2) Nakamoto also teaches that uric acid lowering agents are known to treat hypertension, and allopurinol is a uric acid lowering agent.

Further, the optimization of amounts of known agents to be administered to achieve a desired effect is considered well in the competence level of an ordinary skilled artisan in pharmaceutical science, involving merely routine skill in the art.

Furthermore, it is noted that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454,456, 105 USPQ 233,235 (CCPA 1955.)

It is pointed out that xanthine oxidase inhibitor, inhibits the conversion of xanthine to uric acid, i.e xanthine oxidase inhibitor when employed for treating hypertension reduces uric acid levels in the patient. Maeda et al. also exemplifies that uric acid production was inhibited by xanthine oxidase inhibitor AHPP in a dose dependent manner. Thus, the methods as taught by Maeda et al. necessarily result in reducing uric acid levels as recited in the claims, when the amount of AHPP are modified to achieve desired therapeutic effects

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (b) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 18 is rejected under 35 U.S.C. 103(a) as being unpatentable over Baldwin (US 4,058,614, PTO-892 of record), in view of Baldwin et al. (US 4,032,522, PTO-892 of record).

Baldwin '614 teaches a method of treating hypertension comprising administering xanthine oxidase inhibitor. See abstract; Column 1, lines 21-31.

Baldwin does not teach the particular xanthine oxidase inhibitor, allopurinol in the method therein.

Baldwin et al. '522 teaches that allopurinol acts as a specific inhibitor of the enzyme xanthine oxidase which is responsible for the conversion of hypoxanthine and xanthine to uric acid. See column 1, lines 54-60. Baldwin et al. discloses a method of reducing uric acid in a patient by administering xanthine oxidase inhibitors, trifluoromethylimidazoles. See abstract; column 2. It is also disclosed that the compounds therein are anti-hyperuricemic agents, and exhibit anti-hypertensive activity. See column 5, lines 36-45; column 6, lines 5-52.

It would have been obvious to a person of ordinary skill in the art at the time of invention to administer allopurinol in the method of treating hypertension because 1) Baldwin '614 teaches that xanthine oxidase inhibitors are useful in treating hypertension, and 2) Baldwin et al. '522 teach that allopurinol acts as a specific inhibitor of the enzyme xanthine oxidase. Accordingly, one of ordinary skill in the art at the time of invention would have been motivated to administer allopurinol with reasonable

expectation of success of treating hypertension, since Baldwin et al. '522 teach allopurinol to be functionally equivalent as xanthine oxidase inhibitor.

Response to Arguments

Applicant's arguments have been fully considered, but not found persuasive in view of the new ground(s) of rejections presented in this office action, and as discussed below.

Applicant argues that "the Expert Declarations establish critical objective criteria that would rebut a prima facie case of obviousness. The Declarations make clear that more pertinent and more fully developed prior art relating to uric acid's relationship to hypertension taught away from targeting uric acid. The Declarations establish there was skepticism by experts that lowering uric acid could effectively treat hypertension. At a minimum, the Declarations establish that there was a lack of expectation in the art that uric acid was causative and that administering uric acid lowering medicines could treat hypertension. Accordingly, to the extent that the Examiner believes that the Maeda patent establishes a prima facie case of obviousness, Applicants respectfully assert that the evidence of objective criteria of nonobviousness submitted herewith strongly rebuts obviousness." These arguments have been considered, but not found persuasive. Nakamoto et al. clearly teaches that compounds that lower uric acid are effective in treating hypertension, and Applicant also acknowledges in the instant specification that uric acid was known as a possible risk factor for hypertension. Accordingly, one of ordinary skill in the art at the time of invention would be motivated to optimize the

amounts of xanthine oxidase inhibitor to achieve uric acid levels of 5.0-6.9 mg/dL with reasonable expectation of success of treating hypertension, since as discussed above and further applicant also acknowledges that uric acid was known as a possible risk factor for hypertension.

Applicant argues that "Applicants object to the Patent Office's reliance on the flawed statement in Nakamoto for the allegation that Nakamoto teaches that compounds that lower uric acid are effective in treating hypertension. Applicants provide the comments of Dr. Richard Johnson, included in the attached SECOND DECLARATION OF RICHARD JOHNSON, M.D. (Dr. Johnson, in his own right, being an expert in the of hypertension), which show that the statement made in the Nakamoto patent relied on by the Examiner is so flawed that it would not be given any weight, and indeed was not given weight by those skilled in the art." And further the remarks provided by Dr. Johnson in his declaration that "I have studied the Nakamoto European patent (Nakamoto Patent) cited by the Examiner in the subject application. The Nakamoto patent is directed to a new uricosuric compound; not to a xanthine oxidase inhibitor." These arguments have been considered, but not found persuasive. It is pointed out that both uricosuric agent, and xanthine oxidase inhibitor reduce the amount of uric acid in plasma. Nakamoto clearly teaches that compounds therein that lower uric acid are effective in treating hypertension, and the compounds that lower uric acid include uricosuric compounds, and also xanthine oxidase inhibitors because Nakamoto et al. provides examples of xanthine oxidase inhibitors such as allopurinol,

benzbromarone, probenecid as uric acid lowering agents. Accordingly, there is clear motivation to employ uric acid lowering agents to treat hypertension.

Applicant's remarks that "The cited Nakamoto patent makes statements which in actuality serve to teach away from administering allopurinol. In particular, the Nakamoto patent states that "Allopurinol, benzbromarone and probenecid have been clinically used, but they have various adverse effects and are not satisfactory." These remarks have been considered, but not found persuasive because Nakamoto et al. do not teach away from employment of allopurinol a well known xanthine oxidase inhibitor for reducing uric acid. Rather, Nakamoto teaches that one need to excise caution when allopurinol is continuously administered for a long time.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shobha Kantamneni whose telephone number is 571-272-2930. The examiner can normally be reached on Tuesday-Thursday, 7.30 am-3.30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan, Ph.D can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Shobha Kantamneni, Ph.D
Patent Examiner
Art Unit : 1617

SHEELA RAMANATHAN
SUPERVISORY PATENT EXAMINER